

## Recent Advances in HIV Associated Renal Disease

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### Abstract

Renal disease is becoming an important cause of morbidity and mortality in HIV-affected individuals, as the Highly Active Anti-retroviral Therapy (HAART) has been widely used in HIV-positive patients. HIV infection can cause severe kidney disease directly, including acute kidney injuries, thrombotic micro-angiopathies, HIV-associated Nephropathy (HIVAN), and HIV Immune Complex Kidney Disease (HIVICK) as well as progress to Chronic Kidney Disease (CKD). In this review, we analyze the recent advances in renal complications associated with HIV infection.

**Keywords:** Human immunodeficiency virus; HIV-associated nephropathy; HIV immune complex kidney disease; HIV associated acute kidney injury

### Introduction

Renal disease is becoming an important cause of morbidity and mortality in populations with Human Immunodeficiency Virus (HIV) infection, as HIV infection has a tendency to progress to a chronic disease [1]. With the prevalence of HIV increasing, the size of HIV-infected population and the longevity of HIV-affected patients are increasing due to the Highly Active Anti-retroviral therapy (HAART). HIV infection can cause severe kidney disease directly, including acute kidney injuries, thrombotic micro-angiopathies, HIV-associated Nephropathy (HIVAN), and HIV Immune Complex Kidney Disease (HIVICK). Previously, collapsing Focal Segmental Glomerulosclerosis (FSGS) were thought to be prevalent in HIV-infected patients, but it has been currently appreciated that kidney disease encompassed the entire spectrum of renal pathologies in the HIV population. Rao et al., divided the HIV-1-associated renal parenchymal diseases into four groups [2]: (1) acute tubular dysfunction with electrolytes abnormalities and/or renal failure caused by infections and nephrotoxic drugs; (2) HIV glomerulopathies related to immunological abnormalities (3); HIV-associated thrombotic micro-angiopathies; and (4) HIVAN. In HIV-associated renal disease patients have a higher risk for End Stage Renal Disease (ESRD) than general population. In this review, we highlight the recent advances on the renal complications associated with HIV infection.

### HIV-associated Nephropathy (HIVAN)

HIVAN, first described in 1984, is the most prevalent form of HIV-associated kidney disease. It is a kidney syndrome in HIV-1 seropositive patients, characterized by collapsing focal sclerosing glomerulopathy, heavy proteinuria, kidney dysfunction and rapid progression to kidney failures, which occurs in 2-10% of HIV-infected patients, most often affecting individuals of African descent [3,4]. Histopathological findings include collapsing glomerulopathy, global or focal glomerulosclerosis, microcystic transformation of renal tubules, interstitial inflammation and hyperplasia of podocytes [5]. The risk of kidney disease progression in HIV positive black patients is increased [6-8]. In recent years there have been important advances in understanding the pathogenesis of the disease with some APOL1 polymorphisms described in association with an increased risk for HIVAN and progression to ESRD [9-11].

APOL1 is expressed in podocytes, and the relevance of APOL1 risk alleles in patients of African descent with HIVAN is high, implicating potential podocyte effects [12,13]. And recent genetic

studies implicate the APOL1 G1 and G2 alleles to account in part for this excess of risk [9,11,14]. In addition, AT(1)R and AT(2)R have been reported to play an important role in the progression of HIVAN [15]. The beneficial effects of HAART on HIVAN have been supported by renal biopsy, showing a dramatic improvement of renal histological findings of patients receiving anti-retrovirals [16,17]. Data from several Randomized Controlled Trials (RCT) studies suggest steroids and angiotensin-converting enzyme inhibitors appear to improve kidney function in patients with HIVAN [18]. Early recognition of the disease is crucial to start Combination Antiretroviral Therapy (cART) and renin-angiotensin system blockers before irreversible renal injury [19].

### HIV Immune Complex Kidney Disease (HIVICK)

HIV Immune Complex Kidney Disease (HIVICK) is reported in 21% of hospitalized patients with advanced kidney dysfunction [20]. The racial predilection for HIVICK is conflicting. An early study showed very few black HIV-positive patients with HIVICK based on the results of renal biopsy [21]; another study indicated, 80% of HIV-infected patients being white [22].

However, a recent study of 751 HIV-infected patients in United States showed that HIVICK patients were predominantly African American (92%), HIVICK patients were more likely to have HIV RNA > 400 copies/ml, diabetes, and hypertension. Compared with HIVAN, patients with HIVICK had more antiretroviral therapy exposure, lower HIV viral loads, and higher CD4 and estimated GFR. ESRD incidence is lower in HIVICK patients compared with those with HIVAN.

Unlike HIVAN, cART use was not associated with the incidence of ESRD in HIVICK [23]. HIV viral replication or immune responses to viral proteins may be essential to trigger HIVICK, and the patients associated with hypertension and diabetes should receive a kidney biopsy. In a cohort of African-American patients with biopsy-proven non-HIVAN renal pathology, 76% of patients carrying two APOL1 risk

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alleles had FSGS. In contrast, immune complex GN was found more often on renal biopsy in patients with only one or no APOL1 risk allele (47% and 40%, respectively) [9,24].

### HIV Associated Acute Renal Injury (AKI)

ARF is a clinical syndrome defined as an abrupt decrease in GFR over days to weeks with an increase in serum creatinine level to values > 1.5 mg/dl or > 1.3 times the laboratory upper limit of normal, which returns to baseline values within 3 months [25]. AKI is more common in HIV-infected persons than in the general population. Its presence in HIV infected patients is a risk factor for poor clinical outcomes, and results in lengthened time of hospitalization and a high rate of mortality. This is because that AKI is associated with an increased risk of End Stage Renal Disease (ESRD), cardiovascular disease, heart failure, and death [26]. Hospitalizations of HIV-infected patients that were complicated by AKI were also complicated by much higher in-hospital mortality (27%) than seen in admissions of HIV-infected patients without AKI (4.5%) [27].

On the other hand, some risk factors also contribute to the development of AKI after HIV-infection. These factors include pre-existing Chronic Kidney Disease (CKD), advanced HIV infection (low CD4 + cell count and HIV viral load), HCV co infection, and antiretroviral drugs toxicity, low serum albumin (<3.7 mg/dl), low body mass index (<18.5 kg/m<sup>2</sup>), black race, hypertension, diabetes, cardiovascular disease, hypomagnesemia, male gender and older age [28-30].

### Diffuse Infiltrative Lymphocytosis Syndrome (DILS)

DILS was first reported in 1989 [31]. It is a rare complication of HIV attributed to an antigen- (viral load) driven response of expanded oligoclonal CD8+ lymphocytosis, with consequent organ infiltration that is principally manifested by parotid gland enlargement, sicca syndrome-like symptoms and life-threatening pulmonary infiltration. Renal involvement is characterized by acute tubulointerstitial nephritis with dense cellular infiltrates consisting of lymphocytes, monocytes and plasma cells [32,33].

### Treatment of HIV Associated Renal Disease

Newly introduced Highly Active Anti-retroviral Therapy (HAART) has significantly reduced the incidence of HIVAN in the recent years. The HAART has been found to retard and revert the progression of renal insufficiency towards ESRD, and to increase survival of the patient. A recent large cohort study of 20,132 patients in United Kingdom showed that decreased eGFR of HIV positive patients at baseline is an independent risk factor for all-cause mortality and progression to stages 4-5 CKD, and black HIV-positive patients with eGFR of 30-59 mL/min/1.73 m<sup>2</sup> and white/other HIV-positive patients with eGFR of 30-44 mL/min/1.73 m<sup>2</sup> were at high risk of kidney disease progression, their eGFR should be monitored closely during clinical follow-up [34].

Kidney Transplantation (KT) is an established treatment for ESRD in general population. Recent data have confirmed that KT is increasingly offered to ESRD patients with well-controlled HIV infection. A cohort study showed that KT in HIV-positive patients. In 35 HIV-positive KT recipients, the median CD4 cell count was 366, all had undetectable HIV RNA levels at kidney transplantation, and 44% received a kidney from a live donor. Patient survival at 1 and 3 years was 91.3%, and graft survival rate was 84.7%, but the cumulative incidence of acute rejection was high (48%) [35].

### Conclusion

Renal disease is an increasing cause of morbidity and mortality in HIV-positive patients. Kidney disease encompassed the entire spectrum of renal pathologies in the HIV population. The close monitoring of proteinuria, renal function and the renal biopsy is important in HIV-infected patients. Till now, there is no special therapy for treatment of HIV-associated renal diseases, and however, cART and HAART have beneficial effects on patients with those diseases. In addition, application of angiotensin-converting enzyme inhibitors also improves kidney function in patients with HIVAN.

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